

Departement für Klinische Diagnostik und Services, Abteilung für Anästhesiologie
der Vetsuisse-Fakultät Universität Zürich

Vorsteherin des Departements: Prof. Dr. Regina Hofmann-Lehmann
Leiterin der Abteilung für Anästhesiologie: Prof. Dr. Regula Bettschart-Wolfensberger
Oberärztin der Abteilung für Anästhesiologie: PD Dr. Annette Kutter Brandau

Arbeit unter wissenschaftlicher Betreuung von
Dr. Nadja Sigrist, Leiterin der Abteilung Intensivmedizin

**Correlation of plasmatic coagulation tests and fibrinogen^{Clauss} with ROTEM
parameters and prediction of bleeding in dogs.**

Inaugural-Dissertation

zur Erlangung der Doktorwürde der
Vetsuisse-Fakultät Universität Zürich

vorgelegt von

Nathalie Enk

Tierärztin
von Altstätten, St. Gallen

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Nathalie Enk

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Ziel dieser Studie war es, den Zusammenhang zwischen Fibrinogen_{Clauss} sowie den plasmatischen Gerinnungstests Prothrombinzeit (PT) und aktivierten partiellen Thromboplastinzeit (aPTT) mit Thromboelastometrie-Parametern (ROTEM) in einer Population gesunder und kranker Hunde zu evaluieren und die prognostische Fähigkeit dieser Parameter zur Vorhersage des Blutungsrisikos zu untersuchen.

Signalement, Vorbehandlung, klinische Anzeichen von Blutungen, Fibrinogen_{Clauss}, plasmatische Gerinnungstests, Hämatokrit, Thrombozytenzahl und ROTEM-Ergebnisse wurden retrospektiv aufgearbeitet. Korrelationen zwischen Fibrinogen_{Clauss} und der maximalen Gerinnselfestigkeit (MCF_{FIBTEM}) sowie zwischen PT oder aPTT und den entsprechenden ROTEM-Parametern wurden bestimmt. Die Parameter wurden zwischen Hunden mit und ohne klinische Anzeichen von Blutungen verglichen.

Siebenundneunzig Fälle erfüllten die Einschlusskriterien. Fibrinogen_{Clauss} zeigte eine starke Korrelation zu MCF_{FIBTEM} ($r=0.860$, $n=97$, $P<0.001$). Die extrinsisch aktivierte Gerinnungszeit (CT_{EXTEM}) wies eine starke Korrelation zu PT auf ($r=0.839$, $n=53$, $P<0.001$) und aPTT korrelierte stark mit der intrinsisch aktivierten Gerinnungszeit (CT_{INTEM}) ($r=0.664$, $n=31$, $P<0.001$). Die CT_{INTEM} >149s war 100% sensitiv, um Blutungen vorauszusagen.

MCF_{FIBTEM} kann als eine Alternative verwendet werden, um den Effekt von Fibrinogen auf die Hämostase zu bewerten und CT_{EXTEM} sowie CT_{INTEM} korrelieren stark mit PT und aPTT.

aPTT; Fibrinogen; ROTEM; Hund; PT

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Correlation of plasmatic coagulation tests and fibrinogen_{Clauss} with ROTEM parameters and prediction of bleeding in dogs

The aim of our study was to determine the correlation between fibrinogen_{Clauss} and plasma coagulation tests with rotational thromboelastometry (ROTEM) parameters and to evaluate their ability to predict bleeding in dogs.

Signalement, medical treatment, clinical signs of bleeding, fibrinogen_{Clauss}, plasma coagulation tests results, hematocrit, platelet count, and ROTEM parameters were retrospectively retrieved from patient records. Correlations between fibrinogen_{Clauss} and FIBTEM maximum clot firmness (MCF_{FIBTEM}) and between prothrombin time (PT) or activated partial thromboplastin time (aPTT) and the appropriate ROTEM parameters were determined. Parameters were further compared between dogs with and without clinical signs of bleeding.

Ninety-seven cases met the inclusion criteria. Fibrinogen_{Clauss} showed strong correlation with MCF_{FIBTEM} ($r=0.860$, $n=97$, $P<0.001$). The extrinsic activated clotting time (CT_{EXTEM}) showed strong correlation with PT ($r=0.839$, $n=53$, $P<0.001$) and the intrinsic activated clotting time (CT_{INTEM}) was strongly correlated with aPTT ($r=0.664$, $n=31$, $P<0.001$). An INTEM clotting time >149 s was 100% sensitive to predict bleeding.

In conclusion, MCF_{FIBTEM} can be used to evaluate the effect of fibrinogen on hemostasis as an alternative to determination of fibrinogen_{Clauss}. Additionally, CT_{EXTEM} and CT_{INTEM} are strongly correlated with PT and aPTT, respectively.

aPTT; Canine; fibrinogen; ROTEM; PT

STANDARD ARTICLE

Correlation of plasma coagulation tests and fibrinogen_{Clauss} with rotational thromboelastometry parameters and prediction of bleeding in dogs

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Background: Correlation of plasma fibrinogen concentration (fibrinogen_{Clauss}) with rotational thromboelastometry (ROTEM) parameters has not been investigated in dogs.**Objectives:** To determine the correlation between plasma coagulation tests and fibrinogen_{Clauss} with ROTEM parameters and to evaluate their ability to predict bleeding in dogs.**Animals:** Ninety-seven dogs with concurrent determination of fibrinogen_{Clauss} and fibrin polymerization test (FIBTEM) analysis.**Methods:** Signalment, pretreatment, clinical signs of bleeding, fibrinogen_{Clauss}, plasma coagulation test results, hematocrit, platelet count, FIBTEM, extrinsic (EXTEM) and intrinsic (INTEM) activated ROTEM assays were retrieved retrospectively. Correlations between fibrinogen_{Clauss} and FIBTEM maximum clot firmness (MCF_{FIBTEM}) and between prothrombin time (PT) or activated partial thromboplastin time (aPTT) and ROTEM parameters were determined. Dogs were further assigned to groups with or without clinical signs of bleeding. The prognostic significance of significantly different parameters to predict bleeding was evaluated.**Results:** Fibrinogen_{Clauss} showed strong correlation with MCF_{FIBTEM} ($r = 0.860$, $n = 97$, $P < .001$). PT showed strong correlation with EXTEM clotting time (CT_{EXTEM}) ($r = 0.839$, $n = 53$, $P < .001$), and aPTT was strongly correlated with INTEM CT (CT_{INTEM}) ($r = 0.664$, $n = 31$, $P < .001$). Platelet count, PT/aPTT, EXTEM clot formation time (CFT_{EXTEM}), MCF_{EXTEM}, EXTEM maximum clot elasticity (MCE_{EXTEM}), and CT_{INTEM} were significantly different between groups. A CT_{INTEM} >149 seconds was 100% sensitive to detect bleeding.**Conclusions and Clinical Importance:** The MCF_{FIBTEM} can be used to evaluate the effect of fibrinogen on hemostasis as an alternative to determination of fibrinogen_{Clauss}. In addition, CT_{EXTEM} and CT_{INTEM} are strongly correlated with PT and aPTT, respectively.**KEYWORDS**

aPTT, canine, fibrinogen, FIBTE, PT

Abbreviations: aPTT, activated partial thromboplastin time; AUC, area under the curve; CFT, clot formation time; CT, clotting time; EXTEM, extrinsic-activated ROTEM; Fc, fibrinogen measured by the Clauss method; FIBTEM, fibrin polymerization test; INTEM, intrinsic-activated ROTEM; MCE, maximum clot elasticity; MCF, maximum clot firmness; ML, maximum lysis; PT, prothrombin time; ROC, receiver operating characteristics; ROTEM, rotational thromboelastometry.

1 | INTRODUCTION

Fibrinogen plays a key role in forming a stable and impermeable clot at the site of tissue damage.^{1,2} The linking of fibrinogen to activated platelets is followed by cleavage of fibrinogen to fibrin and its polymerization.^{1,3} Fibrinogen is the 1st factor to become critically decreased during dilutional coagulopathy and perioperative hemorrhage.^{2,4,5} Early recognition of coagulopathy because of hypofibrinogenemia is

important because it is potentially reversible and correction may improve outcome.^{6,7}

Various methods are used to determine plasma fibrinogen concentration, such as the Clauss method, antigen determination, and viscoelastic measurements by means of thromboelastometry.^{8,9} Currently, the most commonly used assay is the fibrinogen Clauss assay (Fc), where a high concentration of thrombin is added to diluted citrated plasma followed by measurement of the clotting time (CT).^{9–12} The CT of fibrinogen is measured by mechanical or photo-optical principles. The mechanical method identifies dissociation of a metal ball from a magnetic field upon clot formation, whereas the photo-optical method records alteration in turbidity.¹² In the mechanical method, time measurement is started after the addition of thrombin reagent to the plasma sample and is stopped when the contact of a steel ball and a magnetic sensor is broken because of its incorporation into the fibrin network.¹³ A predetermined standard curve of CT against fibrinogen concentration is used to read Fc, which is inversely correlated with CT.^{12,14}

Several studies have documented that standard coagulation tests are time-consuming and not effective to identify patients with increased risk of bleeding.^{7,15–17} Rotational thromboelastometry (ROTEM) allows a preliminary evaluation of coagulation within 10 minutes, compared to the 45–60 minutes for plasma coagulation assays, enabling effective implementation of therapeutic interventions.^{10,18,19} The extrinsic-activated ROTEM (EXTEM) assay is activated by proprietary tissue factor, whereas the intrinsic-activated ROTEM (INTEM) assay is activated by ellagic acid and phospholipid. The fibrin polymerization test (FIBTEM) is an EXTEM-based assay with the addition of cytochalasin D to inactivate the platelets.²⁰ The FIBTEM assay indicates the formation and stability of the fibrin clot.²¹ In people, FIBTEM maximum clot firmness (MCF_{FIBTEM}) is used as a parameter representing the functional whole-blood fibrinogen concentration.^{3,11,18}

Correlation of Fc and MCF_{FIBTEM} has been investigated in people and cats but not in dogs.^{3,7,10,19,22–24} The correlation of other thromboelastometry parameters and plasma coagulation tests has been investigated in clinically healthy dogs, showing only moderate correlation.²⁵ The purpose of our study was to determine correlations between Fc and MCF_{FIBTEM} and between the plasmatic coagulation tests prothrombin time (PT) and activated partial thromboplastin time (aPTT) with ROTEM parameters in a population of healthy and sick dogs and to identify factors that influence this correlation. Our hypothesis was that a correlation exists between Fc and plasma coagulation times and ROTEM parameters. Furthermore, the ability of plasma coagulation tests and ROTEM parameters to predict bleeding in dogs was evaluated.

2 | MATERIALS AND METHODS

2.1 | Data collection and classification

The hospital's patient and laboratory databases were searched for ROTEM analysis and Fc determination in dogs between 2013 and 2017. Eligible dogs were of any breed, either sex, and older than 0.5 years. Medical records of identified dogs were checked for simultaneous measurements of Fc and MCF_{FIBTEM} .

Signalment, treatment before analysis (eg, fluid treatment, transfusions, drugs within 3 days before fibrinogen measurement), hematocrit, platelet count, PT, aPTT, Fc, EXTEM-S (EXTEM assay with single-use reagent), INTEM-S (INTEM assay with single-use reagent), and FIBTEM-S (FIBTEM assay with single-use reagent) parameters (CT, measured in seconds; clot formation time [CFT], measured in seconds; MCF, measured in millimeter; and maximum lysis [ML], measured in percentage) were extracted from patient records and included if measurements had been made simultaneously. Fc, PT, and aPTT were determined using a semiautomatic mechanical method (STAGO CH SA, Zurich, Switzerland). The ROTEM-S (ROTEM-Delta; single-use reagent TEM Innovations GmbH, Munich, Germany) analysis was performed following an institutional standard operating protocol based on manufacturer's instructions and international guidelines.^{26–29} Briefly, 300 μ L citrated blood was allowed to stand for approximately 10 minutes in the 37°C warming chamber of the device followed by analysis using an automated pipette and single portion reagents. Samples were analyzed for 60 minutes. The ROTEM tracings were evaluated visually for artifacts and excluded if suspicious. If several measurements of 1 dog were present, the 1st measurement was used.

Based on patient records, dogs were classified as with or without clinical signs of bleeding (bleeding versus non-bleeding group). Bleeding was defined as any visible external bleeding including tissue bleeding, epistaxis, hemoptysis, hematochezia, melena, petechiae or ecchymosis, identification of hemoabdomen or hemothorax (effusion hematocrit >20% or intraoperative diagnosis), or pulmonary or central nervous system changes suspicious for bleeding based on diagnostic imaging (head computed tomography, chest radiographs) together with clinical results and diagnosis. In addition, dogs were classified as hypocoagulable if ≥ 2 results of the following ROTEM parameters were indicative of hypocoagulability based on institutional reference intervals: $MCF_{EXTEM} < 32$ mm, $MCF_{FIBTEM} < 2$ mm, $CT_{EXTEM} > 87$, and $CFT_{EXTEM} > 357$ seconds.³⁰ Hypercoagulability was defined as a decrease in CT_{EXTEM} (<23 seconds) or CFT_{EXTEM} (<85 seconds) or an increase in MCF_{EXTEM} (>65 mm) or a combination of these parameters.³¹ For statistical analysis, an undetectable MCF_{FIBTEM} , identified as a green line, was defined as $MCF_{FIBTEM} = 1$ mm. If MCF_{EXTEM} did not reach the amplitude of 20 mm, CFT_{EXTEM} was defined as 3600 seconds (ie, run time of ROTEM). The definition of hyperfibrinolysis was based on an ML value exceeding the upper reference value of 14%.

2.2 | Data analyses and statistics

Data were manually entered or copied (ROTEM parameters) into a spreadsheet. Statistical analyses were performed using the statistical software package SPSS (IBM SPSS statistics 25.0, Armonk, NY, USA). Continuous data were tested for normality using the Shapiro-Wilk test. Depending on the underlying distribution, data were expressed as mean and SD or median and range. Nonparametrically distributed continuous variables were compared using the Mann-Whitney *U* test. A Student's *t* test was performed to detect differences between patient groups with parametrically distributed continuous variables. The chi-square test was used to evaluate the associations between categorical variables. Correlation of parametric data was assessed

using the Pearson method. For nonparametrically distributed data, Spearman's correlation was used for analysis. The accuracy of standard coagulation tests and ROTEM to determine dogs with clinical signs of bleeding was evaluated using receiver operating characteristics (ROC) and the area under the ROC curve (AUC). You den's J statistic was used to select the optimum cutoff point of the ROC curves. A P -value $< .05$ was considered statistically significant.

3 | RESULTS

The database search identified 108 dogs with concurrent ROTEM and Fc analysis. Nine dogs were subsequently excluded because of lack of simultaneous measurements of Fc and MCF_{FIBTEM}. Two dogs were excluded because ROTEM analysis showed artifacts. Therefore, 97 dogs met the inclusion criteria and were enrolled. The study population included 41 different breeds with Beagles (16.5%), crossbreeds (15.5%), Flat Coated Retrievers (7.2%), and Golden Retrievers (6.2%) being the most common. Sixty-one dogs (62.9%) were female (27 intact, 34 spayed) and 36 (37.1%) dogs were male (27 intact, 9 castrated). Median age was 4.8 years (range, 0.5–14.9 years) and median weight was 18.0 kg (range, 2.2–60.0 kg). Nonsteroidal anti-inflammatory drugs (NSAIDs) had been administered to 8 of 97 dogs (8.2%); of the 97 dogs, 8 (8.2%) had received synthetic vitamin K, 5 (5.2%) had received tranexamic acid, 3 (3.1%) had been treated with fresh frozen plasma, and 2 (2.1%) had received a whole-blood transfusion within 3 days before blood sampling. Forty-seven (48.5%) dogs were considered healthy based on clinical examination and blood analysis results. The remaining 50 (51.5%) dogs had been presented with various diseases.

Of the 66 dogs with an available EXTEM analysis, 25 (37.9%) were defined as hypocoagulable and 8 (12.1%) were defined as

hypercoagulable. Nineteen of 97 dogs (19.6%) had Fc below, and 20 of the 97 (20.6%) dogs had Fc above the reference interval (1.2–2.8 g/L), whereas MCF_{FIBTEM} was < 2 mm (green line) in 17 of the 97 dogs (17.5%; Figure 1). Nine of 66 (13.6%) dogs were considered hyperfibrinolytic.

Correlations among ROTEM parameters, Fc, and plasma coagulation times including subgroup analysis are summarized in Table 1. Fibrinogen_{Clauss} was strongly correlated with MCF_{FIBTEM} ($r = 0.860$, $P < .001$; Figure 1). PT was strongly correlated with CT_{EXTEM} ($r = 0.839$, $P < .001$) and strongly correlated with CFT_{EXTEM} ($r = 0.695$, $P < .001$; Table 1 and Figure 2). For aPTT, the best correlation was found between CT_{INTEM} and aPTT ($r = 0.664$, $P < .001$; Table 1 and Figure 3).

Mean or median ROTEM parameters generated with EXTEM-S, INTEM-S, and FIBTEM-S analysis, and available hematology and coagulation parameters are presented in Table 2. Thirty of 96 dogs (30.9%) had clinical signs of bleeding (bleeding group) with 15 of these (50.0%) being considered hypocoagulable and 13 dogs (43.3%) being thrombocytopenic. Platelet count, PT, aPTT, and the ROTEM parameters including CFT_{EXTEM}, MCF_{EXTEM}, and CT_{INTEM} were significantly different between dogs with and without clinical signs of bleeding (Table 2). The specific parameters and their cutoff values for detecting dogs with clinical signs of bleeding analyzed with ROC are shown in Table 3. The definition of hypocoagulability used showed a sensitivity of 60% and a specificity of 65% to detect bleeding ($P = .04$).

4 | DISCUSSION

Ours is the 1st study to report a strong correlation between Fc and MCF_{FIBTEM} in dogs. PT and aPTT also strongly correlated with CT_{EXTEM} and CT_{INTEM}, respectively.

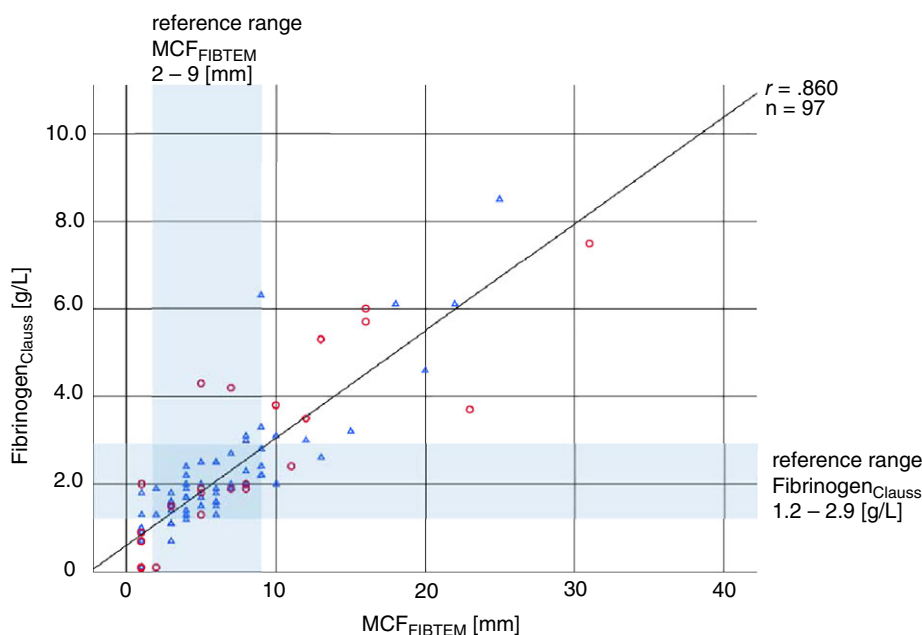


FIGURE 1 Scatter plot showing the correlation between fibrinogen_{Clauss} and MCF_{FIBTEM} in 113 dogs. Linear adjustment is marked. Circles in red and triangles in blue represent dogs with and without clinical signs of bleeding, respectively. Abbreviations: FIBTEM, fibrin polymerization test; MCF, maximum clot firmness; n, number of variables; r, correlation coefficient

TABLE 1 Correlation (r) between plasmatic coagulation tests and ROTEM parameters in dogs and divisions into subgroups

	Fc and MCF _{FIBTEM}			PT and CT _{EXTEM}			aPTT and CT _{INTEM}		
	n/N/%	r	P	n/N/%	r	P	n/N/%	r	P
All values	97/97/100	0.860	.001	53/53/100	0.839	.001	31/31/100	0.664	.001
Hematocrit									
<40%	30/95/31.6	0.940	<.001	22/52/42.3	0.921	<.001	10/31/32.3	0.491	.15
≥40%	65/95/68.4	0.749	<.001	30/52/57.7	0.712	<.001	21/31/67.7	0.035	.88
Platelet count									
<130 (×10 ⁶ /μL)	20/87/23.0	0.855	<.001	17/48/35.4	0.937	<.001	24/29/82.8	0.392	.05
≥130 (×10 ⁶ /μL)	67/87/77.0	0.802	<.001	31/48/64.6	0.602	<.001	5/29/17.2	0.500	.39
Hyperfibrinolysis									
ML _{EXTEM} > 14%	9/66/13.6	0.980	<.001	7/53/13.2	0.964	<.001	1/30/3.3	(–)	(–)
ML _{EXTEM} < 14%	57/66/86.4	0.865	<.001	46/53/86.8	0.764	<.001	29/30/96.7	0.391	.03
Pretreatment									
Yes	19/95/20.0	0.913	<.001	12/51/23.5	0.930	<.001	3/31/9.7	1.000	(–)
No	76/95/80.0	0.840	<.001	39/51/76.5	0.759	<.001	28/31/90.3	0.256	.18

Abbreviations: aPTT, activated partial thromboplastin time; CT, clotting time; EXTEM, extrinsic-activated ROTEM; Fc, fibrinogen measured by the Clauss method; FIBTEM, fibrin polymerization test; INTEM, intrinsic-activated ROTEM; MCF, maximum clot firmness; ML, maximum lysis; PT, prothrombin time; ROTEM, rotational thromboelastometry; (–), no data available.

Similarly, strong correlations between Fc and FIBTEM_{MCF} have been reported in people.^{3,7,10,22–24,32} Compared with the correlation between Fc and MCF_{FIBTEM} in healthy cats ($r = 0.620$; $P = .001$),¹⁹ a stronger correlation was found in our population of both healthy and clinically ill dogs. Including abnormal results, both below and above the reference interval generally leads to a stronger correlation than when all results are distributed in a narrow range, assuming that the 2 parameters are correlated. A correlation between Fc and MCF_{FIBTEM} is expected, because both methods assess fibrinogen cleavage to fibrin. However, they differ in terms of the examined sample (diluted serum versus whole blood with cytochalasin D-inactivated platelets), activator (high dose of thrombin versus tissue factor), end point

determination (1st change in mobility of a metal ball in a magnetic field versus changes in mobility of an oscillating pin), and output (CT [seconds] proportional to predetermined fibrinogen concentration [g/L] versus maximal clot firmness in millimeters).^{11–13,33}

Discrepancies in correlation may be explained by the different end points that are measured by the 2 methods. Although the fibrinogen concentration is the major determinant of MCF_{FIBTEM}, it also depends on the availability of factor XIII^{34,35} and involves the activity of coagulation factors of the extrinsic pathway, functional fibrinogen, and erythrocytes, and therefore evaluates additional effects of blood cellular components on clot strength.^{36–38} Importantly, although the method of Clauss estimates fibrinogen concentration based on CT,

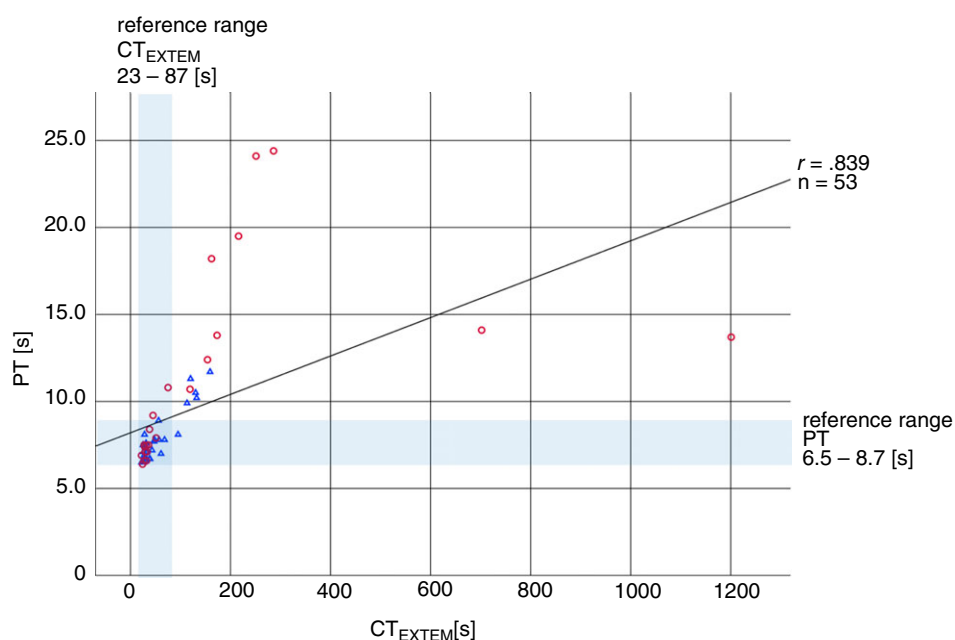


FIGURE 2 Correlation between PT and CT_{EXTEM} in 53 dogs. Linear adjustment is marked. Circles in red and triangles in blue represent dogs with and without clinical signs of bleeding, respectively. Abbreviations: CT, clotting time; EXTEM, extrinsic-activated rotational thromboelastometry; n, number of variables; PT, prothrombin time; r, correlation coefficient

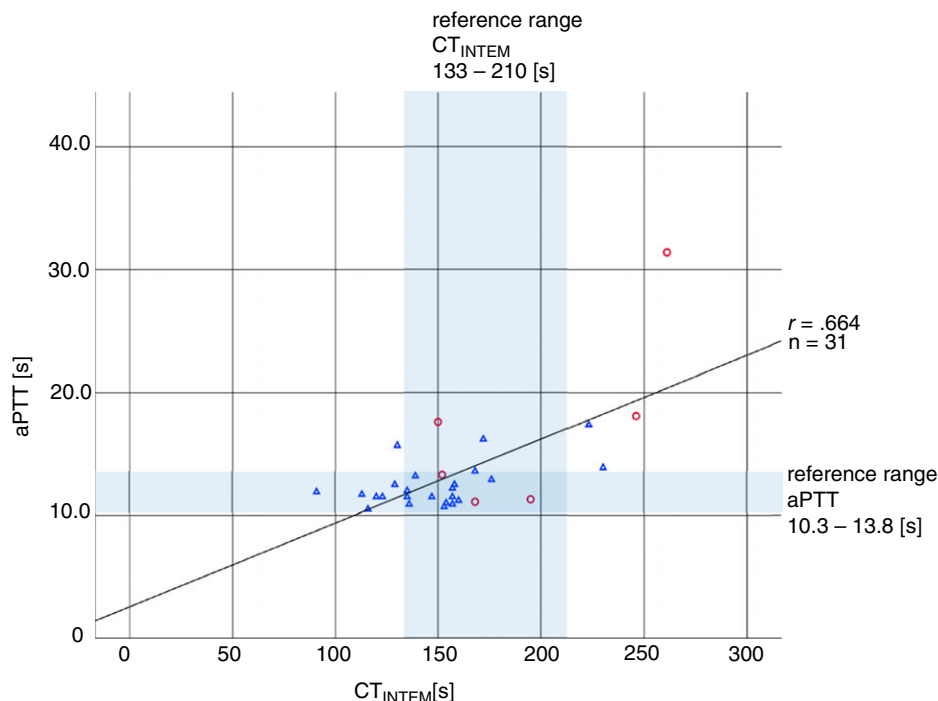


FIGURE 3 Correlation between aPTT and CT_{INTEM} in 31 dogs. Linear adjustment is marked. Circles in red and triangles in blue represent dogs with and without clinical signs of bleeding, respectively. Abbreviations: aPTT, activated partial thromboplastin time; CT, clotting time; INTEM, intrinsic-activated rotational thromboelastometry; n, number of variables; r, correlation coefficient

the FIBTEM-S assay does not provide a fibrinogen concentration but visualizes the clot that forms from cross-linked fibrin strands, erythrocytes, and factor XIII.³⁶ In contrast to fibrinogen determined by the Clauss method, MCF_{FIBTEM} represents a stable clot and requires functional fibrinogen that is not only cleaved to fibrin polymers but also

cross-linked.¹¹ The FIBTEM-S assay further provides additional information regarding the clot strength and clot lysis.³³ The MCF_{FIBTEM} therefore is believed to predict the function of fibrinogen better rather than Fc and is increasingly used for guidance of fibrinogen treatment in people.^{37,39,40}

TABLE 2 Descriptive statistics and comparison between dogs with and without clinical signs of bleeding

Parameter (unit)	Reference interval	Total population (n = 97)	Non-bleeding group (n = 66)	Bleeding group (n = 30)	P-value
Hematology					
Hematocrit (%)	40-55	44 (16-60) [95]	46 (18-60) [65]	36 ± 9 [29]	.001
Platelet count (×10 ⁶ /μL)	130-394	225 ± 115 [87]	256 ± 104 [61]	146 ± 106 [25]	.001
Standard coagulation tests					
Fc (g/L)	1.2-2.9	1.9 (0.1-8.5) [97]	1.9 (0.1-8.5) [66]	1.9 (0.1-7.5) [30]	.39
PT (s)	6.5-8.7	7.5 (6.4-24.4) [83]	7.4 (6.5-11.7) [58]	8.8 (6.4-24.4) [24]	.004
aPTT (s)	10.3-13.8	12.2 (8.9-200.0) [83]	11.9 (8.9-19.0) [58]	15.7 (11.1-200.0) [24]	.001
EXTEM-S assay					
CT _{EXTEM} (s)	23-87	44 (22-1201) [66]	41 (22-159) [36]	45 (22-1201) [29]	.28
CFT _{EXTEM} (s)	85-357	210 (22-3600) [65]	153 (23-2935) [36]	313 (22-3600) [28]	.04
MCF _{EXTEM} (mm)	32-65	45 ± 18 [66]	50 ± 15 [36]	40 ± 17 [29]	.01
ML _{EXTEM} (%)	0-12	2 (0-100) [66]	1 (0-30) [36]	2 (0-100) [29]	.06
INTEM-S assay					
CT _{INTEM} (s)	133-210	157 ± 31 [32]	149 ± 31 [24]	190 ± 46 [7]	.01
CFT _{INTEM} (s)	59-201	71 (35-551) [32]	66 (35-520) [24]	82 (35-551) [7]	.25
MCF _{INTEM} (mm)	52-71	64 (32-83) [32]	64 (32-80) [24]	58 ± 18 [7]	.87
FIBTEM-S assay					
MCF _{FIBTEM} (mm)	2-9	5 (1-31) [97]	5 (1-25) [66]	5 (1-31) [30]	.34

Abbreviations: aPTT, activated partial thromboplastin time; CFT, clot formation time; CT, clotting time; EXTEM, extrinsic-activated rotational thromboelastometry; Fc, fibrinogen measured by the Clauss method; FIBTEM, fibrin polymerization test; INTEM, intrinsic-activated rotational thromboelastometry; MCF, maximum clot firmness; ML, maximum lysis; PT, prothrombin time.

Number of variables within a subgroup is shown in square brackets.

TABLE 3 Parameters for detecting dogs with clinical signs of bleeding analyzed with ROC

Parameter	n	Cutoff value	Sensitivity (%)	Specificity (%)	AUC	P-value
Platelet count ($\times 10^6/\mu\text{L}$)	86	196	76.0	77.0	0.775	.001
Fc (g/L)	96	0.95	36.7	93.9	0.554	.39
PT (s)	82	10.6	45.8	96.6	0.705	.004
aPTT (s)	82	16.25	50.0	96.6	0.767	.001
CT _{EXTEM} (s)	65	133	34.5	97.2	0.577	.28
CFT _{EXTEM} (s)	64	221	67.9	63.9	0.650	.04
MCF _{EXTEM} (mm)	65	51	75.9	61.1	0.685	.01
CT _{INTEM} (s)	32	149	100.0	50.0	0.789	.02
CFT _{INTEM} (s)	32	68	85.7	54.2	0.646	.24
MCF _{INTEM} (mm)	32	37	28.6	95.8	0.524	.85
MCF _{FIBTEM} (mm)	96	2.5	40.0	87.9	0.560	.34

Abbreviations: aPTT, activated partial thromboplastin time; AUC, area under the curve; CFT, clot formation time; CT, clotting time; EXTEM, extrinsic-activated rotational thromboelastometry; Fc, fibrinogen measured by the Clauss method; FIBTEM, fibrin polymerization test; INTEM, intrinsic-activated rotational thromboelastometry; MCF, maximum clot firmness; PT, prothrombin time; ROC, receiver operating characteristics.

An additional explanation for decreased correlation may be a residual platelet effect on MCF_{FIBTEM} that becomes more important the more hypofibrinogenemic a patient becomes.²¹ In addition, anemia may lead to a hypercoagulable FIBTEM tracing because of higher concentrations of coagulation factors in a whole-blood sample with a decreased hematocrit, whereas Fc is not affected by hematocrit.^{25,41} In our study, correlation of Fc with MCF_{FIBTEM} was higher in blood samples with a hematocrit below the reference interval. In contrast to Fc, MCF_{FIBTEM} depends on hematocrit⁴² and an effect on correlation with changes in hematocrit is expected. Both correlations were assessed as strong to very strong; therefore, the clinical importance of hematocrit changes remains to be determined.

Of note, some dogs with Fc within the reference interval did not show clotting in the FIBTEM-S analysis (green line). Again, this observation can be explained by the different measurement end points and implies that fibrinogen is present and to some degree functional, but a stable clot cannot be formed. The addition of thrombin in excess (as used in the Clauss method) to some extent overcomes inhibiting factors of clot generation that may lead to a decrease in MCF_{FIBTEM}.^{11,43} In these cases, the fibrinogen concentration is overestimated by the Clauss method in relation to MCF_{FIBTEM}.^{11,43}

Other reasons for a lack of correlation are test interference by dysfunctional fibrinogen protein in the blood sample, hyperfibrinolysis of circulating fibrin, or a deficiency of factor XIII.^{10,44–46} During fibrinolytic treatment or in hyperfibrinolytic conditions, fibrin or fibrinogen degradation products inhibit fibrin polymerization, leading to a relatively low fibrinogen concentration as measured by the Clauss method.^{47–49} However, MCF_{FIBTEM} theoretically also should be blunted by fibrin degradation products, and the correlation in hyperfibrinolytic dogs was better than in the whole population. Fibrinogen degradation products were not measured in our study, and because dogs with hyperfibrinolysis showed an even stronger correlation of Fc with MCF_{FIBTEM}, hyperfibrinolysis as a cause of the low MCF_{FIBTEM} compared to normal Fc concentration seems unlikely. However, because of the low number of dogs experiencing hyperfibrinolysis, we believe that this result should be interpreted with caution. Overall, MCF_{FIBTEM} can be used in dogs to approximate the plasma fibrinogen concentration and function as described in people and in cats.^{19,21}

We also found a very strong correlation between CT_{EXTEM} and PT and a strong correlation between aPTT and CT_{INTEM}. The identified correlations are stronger than previously described in healthy dogs.²⁵ Again, this finding can be explained by the fact that correlations become stronger when more diverse results are included in the analysis. A correlation between PT and aPTT with CT_{EXTEM} or CT_{INTEM} is expected despite different measurement methods of CT. Both plasma-based coagulation tests and ROTEM CT evaluate the activity of soluble coagulation factors. Prothrombin time measures the time it takes for plasma to clot after addition of thromboplastin and calcium ions. Time measurement stops when the small metal ball of the device gets out of an electromagnetic field because of fibrin fiber formation. The measuring method of aPTT is identical; but instead of thromboplastin, phospholipids are added.⁵⁰ At that time, approximately 5% of the total thrombin has been generated.⁵¹ In contrast, CT_{EXTEM/INTEM} represents the time from activation of the extrinsic pathway by tissue factor or ellagic acid to the start of clot building in a whole-blood sample and evaluates the initiation phase of thrombin generation.⁵² Notably, CT is measured in whole blood and involves interaction with platelets and red blood cells. Again, the presence of red blood cells is expected to influence viscoelastic coagulation test results²⁵ and explain some of the discrepancies in correlation.

The comparison of dogs with and without clinical signs of bleeding and possible anticipation of probability to bleed based on coagulation parameters including ROTEM parameters was an additional aim of our study. Hematocrit and platelet count were lower in dogs with bleeding compared to dogs in the non-bleeding group.

The significantly lower hematocrit was attributed to hemorrhage, but we cannot exclude other reasons for anemia. Although the mean platelet count was significantly lower in the bleeding group, both groups had platelet counts within the reference interval, implying that the lower platelet count was not the main reason for bleeding. In contrast, the median standard plasma coagulation tests PT and aPTT were both significantly prolonged in bleeding dogs and above the reference interval in 50% of the bleeding dogs. Prolongations in PT and aPTT can be the cause or result of bleeding, and neither of the parameters showed good sensitivity for the detection of bleeding. However,

specificity was high, indicating that patients with PT and aPTT within the reference interval are unlikely to bleed.

Because viscoelastic tests involve interaction of coagulation factors with platelets, they are expected to be superior in identifying a bleeding tendency in patients with complex hemostatic disorders. However, although the ROTEM parameters CFT_{EXTEM}, MCF_{EXTEM}, and CT_{INTEM} were significantly different between bleeding and non-bleeding dogs, many bleeding dogs had results within the reference intervals. Although the specificity to exclude bleeding if parameters were within the reference interval was reasonably high, the sensitivity to detect bleeding was low. However, CT_{INTEM} >149 seconds was 100% sensitive to detect bleeding, despite a specificity of 50%. Few studies have focused on prediction of bleeding by use of viscoelastic coagulation assays in dogs.^{53,54} In a previous study, investigators demonstrated that tissue factor-activated thromboelastography, the analogue of EXTEM, correctly identified dogs with clinical signs of bleeding.⁵³ Although the ROC curve of MCF_{EXTEM} showed a high AUC (0.685) in our population, MCF_{EXTEM} does not seem to be a clinically useful individual parameter because of low sensitivity and specificity.

Because bleeding can be caused by the lack or deficiency of any factor or mechanism of hemostasis, it seems prudent that in a heterogeneous population of dogs with bleeding, a single parameter is not helpful to predict bleeding. Because ROTEM allows examination of many aspects of hemostasis in whole blood, a combination of ROTEM parameters, which evaluate the different steps of hemostasis, is expected to be superior to predict bleeding. However, the definition of hypocoagulability used in our study, as well as in previous studies,^{30,31,55,56} did not identify a useful sensitivity to predict bleeding. We suspect that a more complex scoring system is needed to predict bleeding in dogs, similar to that described in people.⁵⁷

Being retrospective in nature, our study has several limitations. Dogs were included if they had concurrent Fc and FIBTEM analysis and standard coagulation tests, and EXTEM and INTEM assays were not additionally available for all dogs. Subgroup analysis and the CT_{INTEM}/aPTT correlation therefore should be interpreted with caution and requires larger studies to identify confounding factors. Furthermore, because we examined a heterogeneous population of clinically ill dogs, some dogs were pretreated with fluids or other medications, including NSAIDs, which may have had an effect on the test results. Because correlation was improved when pretreated patients were compared to untreated dogs, we believe this effect is negligible and potentially affected both tests. Additional studies are needed to evaluate the impact of confounding factors in more detail. As a 3rd limitation, our diagnosis of bleeding was based on clinical signs and we therefore cannot make any statement regarding bleeding that was not clinically apparent.

In conclusion, MCF_{FIBTEM} can be used to evaluate the effect of plasma fibrinogen on hemostasis as an alternative to determination of Fc. In addition, CT_{EXTEM} and CT_{INTEM} were strongly correlated with PT and aPTT, respectively, and can be used to assess the extrinsic and intrinsic pathways of clot formation. None of the assessed parameters could predict bleeding with both high sensitivity and high specificity. However, CT_{INTEM} >149 seconds was 100% sensitive to detect bleeding therefore could be used more frequently for identification of coagulation disorders in the future.

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CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

The study retrospectively analyzed data from clinical patients that were not part of a study (no approval needed). The healthy dogs included were used for institutional reference interval determination approved by the Swiss federal ethics committee on animal research of the Canton of Zurich (#072/2011).

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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